Exploring dissatisfaction with treatment of hypothyroidism: coexistent diseases and treatment preferences

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ABSTRACT

Context: Levothyroxine (LT4) monotherapy is the standard of care for treating hypothyroidism. However, some patients do not feel well and express interest in other therapies.

Objective: To inform the discussion at a symposium addressing treatment for hypothyroidism, we wished to determine perceptions of patients regarding their treatment for hypothyroidism.

Design: An online survey was created to obtain patient's perceptions. Respondents were asked to rank satisfaction with their treatment for hypothyroidism, satisfaction with their treating physician, perceived physician knowledge about hypothyroidism treatments, perceived need for new treatments for hypothyroidism, and perceived life impact of hypothyroidism on a scale of 1 to 10. Respondents were asked to report the type of thyroid hormone they were taking, which was categorized as LT4, LT4 and liothyronine (LT4 + LT3), or desiccated thyroid extract (DTE). They also reported sex, age, cause of hypothyroidism, duration of treatment, medical history, and prevalence of symptoms or side effects.

Participants: A convenience sample of survey respondents with self-reported hypothyroidism.

Results: A total of 12,146 individuals completed the survey. Among respondents without self-reported depression, stressors or medical conditions (n=3670), individuals taking DTE reported a higher median treatment satisfaction of 7 (interquartile range (IQR): 5,9) and a higher physician satisfaction of 7 (IQR: 4,9) compared to other treatments. For LT4 treatment, satisfaction was 5 (IQR: 3,7) and physician dissatisfaction was 6 (IQR: 3,8). For LT4 + LT3 treatment, satisfaction was 6 (IQR: 3,8) and physician satisfaction was 6 (IQR: 3,8). Respondents taking DTE were also less likely to report hypothyroidism-associated side effects related to weight management, fatigue/energy levels, mood, and memory/other cognitive problems, compared to those taking LT4 or LT4 + LT3. The study design does not permit investigation of why patients taking DTE reported best perceived outcomes.

Conclusions: Despite the limitations of the study and the potential for sampling bias, data from this large convenience sample of hypothyroid individuals revealed generalized dissatisfaction with treatment and physicians; patients taking DTE reported best perceived outcomes. Future studies into what constitutes euthyroidism and what determines satisfaction with therapy are needed.

INTRODUCTION

Hypothyroidism is a common endocrine problem that results from insufficient secretion of thyroid hormones due to an underactive thyroid gland; it requires lifelong treatment with thyroid hormone replacement therapy.[1] Currently, the standard of care to treat hypothyroidism is daily administration of levothyroxine (LT4), at doses that normalize serum thyroid stimulating hormone (TSH).[2,3] Even though thyroxine (T4) is intrinsically active in some settings[4], many tissues have deiodinases that activate T4 to triiodothyronine (T3), the biologically active thyroid hormone. The prevailing viewpoint is that a dosage of LT4 that normalizes serum TSH also normalizes serum and tissue T3 levels.[5] Endocrinologists' offices are frequently visited by hypothyroid patients that remain symptomatic despite being "appropriately" treated, complaining of sluggishness, lethargy, sleepiness, memory problems, depression, cold intolerance, hoarseness, dry skin, body weight gain, and constipation.[1] Anecdotally, we know that these patients switch physician multiple times and many use unconventional therapies, such as dietary supplements, nutraceuticals and over-the-counter products.

Most patients with hypothyroidism experience resolution of their symptoms with standard therapy. However, 10 to 15% more of LT4-treated patients have poor quality of life compared with control individuals.[6] The existence of patients with hypothyroidism who are symptomatic despite LT4 treatment that has normalized their TSH values has lead to questions regarding the efficacy of monotherapy with LT4 for all patients.[3,7] We now know objectively that in LT4-treated patients that exhibit a normal serum TSH there is a 15-20% decrease in the ratio of circulating T3/T4[8]; and about 15% of these patients do not maintain normal serum T3 levels.[9] This is hypothesized to be the result of differences in D2 regulation between the hypothalamus and peripheral tissues, as has been shown in a hypothyroid rat model.[10] That replacement with LT4 does not fully restore all aspects of euthyroidism is supported by the observation that females taking LT4 have lower energy expenditure compared to euthyroid women with similar age and body mass index.[11] In addition, NHANES data indicate that individuals taking LT4, with TSH values within the normal reference range, have a higher BMI despite reporting lower calorie intake corrected by body weight, report lower physical activity levels, and are more often taking statins, beta-blockers, and antidepressants compared to euthyroid participants matched by age, gender and race/ethnicity.[8] They also report increased frequency of episodes of memory problems/confusion and are less likely to report being in excellent/good health.[12]

Few physicians are willing to prescribe combination LT4 plus liothyronine (LT3) to manage residual symptoms;[13] and minimal information is available to describe prescription patterns of desiccated thyroid extract (DTE, a porcine-derived thyroid hormone replacement containing both T4 and T3). However, it is not clear that combination therapy is superior to monotherapy in managing hypothyroidism. A total of 14 double blind placebo controlled trials provided heterogeneous results with respect to health-related quality of life and mood and neurocognitive functioning; but there was a patient preference for combination therapy in some of the trials.[6,14-26] In an attempt to query patients, a Danish internet-based questionnaire surveyed 293 individuals on combination therapy, revealing that 84% of patients who had residual symptoms while on monotherapy perceived improved symptoms after switching to combination therapy and 81% stated a clear preference for continuing combination therapy.[27]

The objective of the current study is to analyze the results of an online survey conducted in the spring of 2017 which assessed perceptions of hypothyroid patients regarding treatment effectiveness and their satisfaction with physicians. Approximately 12,000 individuals taking LT4 monotherapy, combination therapy with LT4 and LT3, or desiccated thyroid extract, completed the survey which was posted on the American Thyroid Association (ATA)'s web site.

MATERIALS AND METHODS

Study participants

A convenience sample of hypothyroid individuals was solicited to participate in an online English language survey to determine their perceptions regarding the treatment that they received for hypothyroidism. Participants were asked to report which thyroid hormone they were currently taking for treatment of hypothyroidism, demographic characteristics, etiology and duration of hypothyroidism, and concomitant medical conditions.

Survey Development and Distribution

The Hypothyroidism Treatment Survey was created by the program committee members of the Satellite Symposium on Hypothyroidism organized by the ATA that occurred in the Spring of 2017 in Orlando FL. The program committee members deemed it important to describe the patient perspective regarding hypothyroidism treatment and share the results with program registrants. The survey questions were created to identify demographic and treatment characteristics of individuals being treated for hypothyroidism, coupled with information about their satisfaction with their therapy.

Participants were asked to provide their gender, age (categorized as under 40, 41-50 years old, 51-60 years old, 61-70 years old, or over 70 years old), cause of their hypothyroidism (categorized as Hashimoto's/autoimmune disease, surgery/removal of thyroid, radioactive iodine (RAI) for overactive thyroid, I do not know, or other), and duration of hypothyroidism treatment (categorized as less than one year, 1-5 years, 6-10 years, more than 10 years). To recognize confounding conditions that may contribute to symptoms overlapping with those of hypothyroidism, participants were asked if stress or other medical problems could be contributing to their symptoms and were asked to identify any relevant medical problems that they had (including heart disease, lung disease, diabetes, bone or muscle disease, gastrointestinal disease, cancer (that is not thyroid cancer), thyroid cancer, and depression).

Treatment was defined as taking a thyroid hormone for hypothyroidism; individuals were asked to select the type of thyroid hormone they were taking (categorized as levothyroxine, [including generic or branded forms of levothyroxine], levothyroxine and LT3 [liothyronine, Cytomel], natural thyroid or desiccated thyroid extract [Armour Thyroid, Nature-Throid], I do not know, or other [with the option to specify the thyroid hormone treatment]). The three treatments subjected to further analysis were levothyroxine (LT4), levothyroxine and LT3 (LT4+LT3), and desiccated thyroid extract (DTE). Perception regarding treatment was examined by asking participants to rank, on a scale of 1 to 10, their satisfaction with treatment and with the current physician treating their hypothyroidism (1=not satisfied, 10=completely satisfied), the perceived knowledge of their physician about treatment of hypothyroidism (1=not at all knowledgeable, 10=very knowl-

edgeable), their assessment of the need for new treatments for hypothyroidism (1=no need, 10=strong need), and the impact of hypothyroidism on their life (1=not affected, 10=strongly affected). In addition to reporting the median, 25th, and 75th percentile of the responses, the distribution of the responses was also presented in graphic form. Additional questions were added to assess participant's experiences with their medical care for hypothyroidism; respondents were asked to categorize the number of times they changed physician because they were not satisfied with their hypothyroidism treatment (categorized as none, 1 time, 2-4 times, 5-9 times, or 10 or more times), identify relevant aspects of their life affected by hypothyroidism/thyroid hormone treatment (categorized as weight management, fatigue or energy levels, mood, and memory or other problems with thinking), and prevalence of seeking alternative form of hypothyroidism treatment, not prescribed by your doctor (yes/no).

The survey (available in the Supplemental Materials and Methods) was available online from 1/28/2017 to 3/30/2017. A link to the survey was posted on the ATA website and distributed via email to patients within the ATA database and to the members of the ATA Alliance for Thyroid Patient Education. Members of the ATA were encouraged to further distribute the survey by sharing on group websites and social media. Additionally, the link was included in the Signal eNews, a monthly newsletter emailed to ATA members. No identifying or protected health information was collected from participants. Only IP address was recorded for the purpose of eliminating duplicate responses.

Initial analysis was conducted on the total sample (comprised of respondents taking LT4, LT4 + LT3, or DTE). In addition, four subgroups were created based on disease characteristics in order to further analyze perceptions regarding treatment of hypothyroidism according to the 3 treatments. These groups were as follows: **Subgroup-1**: respondents without self-reported depression, stress or medical conditions; **Subgroup-2**: due to difference in age, gender, and hypothyroid treatment between respondents taking LT4, LT4 + LT3, and DTE a matched subgroup of females was created - those taking LT4 and DTE (the tw largest groups of respondents) were matched 2:1 by age, hypothyroidism treatment, etiology of hypothyroidism, and treatment duration to individuals taking LT4+LT3 (the smallest group of respondents) to account for baseline differences; **Subgroup-3**: respondents with depression but no reported life-stressors or medical conditions; and **Subgroup-4**: respondents with thyroid cancer but no self-reported depression, life-stressors or medical condition.

Statistical methods

Analyses were completed with IBM SPSS Statistics (version 22.0). Both frequency (percent) and median (interquartile range [25th, 75th percentile]) were used to describe the data. The Kruskal Wallis test was used to compare difference in ranked median perception across the three medication treatment groups (LT4 vs LT4+LT3 vs DTE). If a significant difference was observed, the Mann-Whitney U test was used to perform between group analyses. The chi-square test of association was utilized to determine difference in categorical variables across the three medication treatment groups (LT4 vs LT4+LT3 vs DTE). Due to the multiple comparisons performed, a conservative p value of <0.001 was utilized to identify statistically significant differences between groups. This rigorous p value was chosen in order to avoid over-interpreting results in the setting of a survey-based dataset.

RESULTS

A total of 12,146 respondents completed the survey and all subsequent analyses were performed based on the self-reported responses to questions about medical history and hypothyroidism treatment. We excluded 53 respondents that were not taking medication for hypothyroidism. Of the remaining 12,093 individuals (Supplement Table 1), 485 were excluded because they were taking a medication for hypothyroidism other than LT4, LT4 + LT3, or DTE. An additional 442 were excluded due to survey completion from the same IP address and concern that the data represented duplicate surveys. As a result, the total sample of respondents that was further analyzed comprised 11,166 individuals (Figure 1).

The female/male ratio of respondents was approximately 21:1 and age was relatively evenly distributed across the four age categories (Table 1). The most prevalent cause of hypothyroidism was Hashimoto's/autoimmune disease (43%); however, 34% of respondents identified another cause other than Hashimoto's/RAI/surgery or were unsure of hypothyroidism etiology (Table 1). Only 7% of individuals were treated for hypothyroidism for less than one year; the majority (63%) had been on treatment for more than 6 years. One-third of patients stated that their current stress level could be contributing to hypothyroid-related symptoms; another third reported co-existing medical conditions, with the most common one being depression (27%). Only 6% of respondents self-reported depression without any other comorbidities (Table 1).

Within the total sample, 6,949 individuals were taking LT4 monotherapy, 978 reported taking combination LT4+LT3, and 3,239 received DTE (Table 1). When considering perceptions regarding their treatment for hypothyroidism, the median response indicating treatment satisfaction was 5 (25^{th}-75^{th} percentile interval: 3, 8) (Table 1). Among those who were frustrated with their hypothyroidism treatment, the relevant areas identified as causing dissatisfaction were weight management (69%), fatigue or energy level (77%), mood (45%), and memory or other problems thinking (58%). The median response describing satisfaction with the patient's current physician was 6 (25^{th}-75^{th} percentile interval: 3,6) and assessment of the doctor/physician knowledge regarding hypothyroidism treatment was 5 (25^{th}-75^{th} percentile interval: 3, 8); 54% of the sample reported changing physicians more than twice because of dissatisfaction with treatment. Almost all respondents believed that there was a strong need for new treatments for hypothyroidism (median 10 (25^{th}-75^{th} percentile interval: 8,10)) and perceived a significant influence of hypothyroidism on life (median 10 (25^{th}-75^{th} percentile interval: 8,10)) (Table 1).

Next, multiple analyses were utilized to compare the responses within the total sample according to their specific treatment (Table 2). When examining the three treatment sub-groups, the distribution of gender, age, etiology and treatment duration were significantly different. Individuals treated with DTE had the highest median satisfaction with treatment (7 (25^{th}-75^{th} percentile interval: 4,8)) compared to those taking LT4 (5 (25^{th}-75^{th} percentile interval: 3,7)) or LT4+LT3 (5 (25^{th}-75^{th} percentile interval: 3,7)). In particular, as shown in the graphic representations, the distribution of responses was markedly different between those taking DTE versus LT4 (Table 2); individuals on DTE predominately responded positively with an upward trend, such that responses were more frequent at the positive end of the scale. Conversely, individuals on LT4 were more likely to respond negatively, exhibiting a distribution with a downward trend, such that responses were more frequent at the negative end of the scale (Table 2). This varied distribution

between groups can also described by examining the number of patients who ranked satisfaction with treatment as not satisfied (ranked 1 or 2) or completely satisfied (ranked 9 or 10); approximately 20% of respondents taking LT4 and LT4+LT3 were not satisfied with treatment while 14% of DTE users were not satisfied. In comparison, 22% of DTE users were completely satisfied compared to 10% of LT4 and LT4+LT3 respondents (Supplementary Figure 1). Individuals taking DTE were less likely to report problems with weight management, fatigue/energy level, mood, or memory when compared to those taking LT4 or LT4+LT3 (Table 2). Individuals taking DTE had a higher median satisfaction with their current physician (7 (25^{th}-75^{th} percentile interval: 4,9)) compared to those taking LT4 (5 (25^{th}-75^{th} percentile interval: 3,8)) or LT4+LT3 (6 (25^{th}-75^{th} percentile interval: 3-8)); perceived physician knowledge was slightly higher in the DTE subgroup, compared with the LT4 subgroup (Supplementary Figure 2 and 3). Of note, 29% and 21% of individuals taking DTE and LT4+LT3 changed doctors ≥ 5 times because they were not satisfied with their treatment, compared to only 7% of respondents taking LT4. Those taking DTE or LT4+LT3 were more likely to have tried alternative treatment forms not prescribed by their doctor and thought their lives had been more affected by hypothyroidism (10 (25^{th}-75^{th} percentile interval: 9-10)), although this latter parameter was very high in all three subgroups (Table 2 and Supplementary Table 4).

Analyses of Subgroups-1-4

Subgroup-1 (Supplement Table 2, n=3,670) captures respondents without self-reported depression, life-stressors or medical conditions. Those taking LT4 had a median reported treatment satisfaction of 5 (25^{th}-75^{th} percentile interval: 3,7) (Table 3). Their perception regarding treatment of hypothyroidism were as follows: physician satisfaction of 5 (25^{th}-75^{th} percentile interval: 3,8) and physician knowledge of 5 (25^{th}-75^{th} percentile interval: 3,8). Individuals taking combination therapy with LT4+LT3 experienced slightly higher treatment satisfaction (6 (25^{th}-75^{th} percentile interval: 3,8), with similar physician satisfaction and perceived physician knowledge. Respondents taking DTE had the highest scores in treatment satisfaction (7 (25^{th}-75^{th} percentile interval: 5,9)) and physician satisfaction (7 (25^{th}-75^{th} percentile interval: 4,9)). Regardless of treatment modality, all respondents ranked at the highest level (9-10) the need for new treatments and the perception of how much their lives had been affected by hypothyroidism (Table 3). Additionally, respondents taking DTE were less likely to report weight management concerns, fatigue/low energy levels, mood issues, or memory problems compared to those on LT4 or LT4+LT3 (Table 4).

Subgroup-2 (Supplement Table 3, n=1535) is a matched subset of **Subgroup-1** with the respondents taking LT4 and DTE being matched 2:1 by gender (only female respondents), age, etiology of hypothyroidism, and treatment duration to individuals taking LT4+LT3. The matching resulted in the size of the groups being reduced to 1535 respondents (Table 3). Despite the matching, the results obtained in **Subgroup-2** remained very similar to **Subgroup-1** (Table 3 and Table 4).

Subgroup-3 (Supplement Table 4, n=679) respondents, who reported depression, but did not report stressors or other medical conditions, in general ranked lower on all parameters when compared to other subgroups. The median perception of those taking LT4 regarding treatment satisfaction was 4 (25^{th}-75^{th} percentile interval: 1,6), physician satisfaction was 5 (25^{th}-75^{th} per-

centile interval: 2,7) and physician knowledge was 4 (25^{th}-75^{th} percentile interval: 2,6) (Table 3). Individuals on LT4+LT3 reported similar perceptions (Table 3). Respondents taking DTE had the highest scores for: treatment satisfaction 5 (25^{th}-75^{th} percentile interval: 3,7)) and physician satisfaction 6 (25^{th}-75^{th} percentile interval: 3,8), albeit lower than Subgroups 1-2. Perception of physician knowledge remained low (4 (25^{th}-75^{th} percentile interval: 2,8)), similar to other treatment groups. Respondents using all treatment modalities ranked at the highest level (10) the need for new treatments and the perception of how much their lives had been affected by hypothyroidism (Table 3). Within this group, respondents taking DTE were less likely to report fatigue/low energy levels and memory problems compared to those on LT4 or LT4+LT3, though the difference did not reach the statistical significance criterion of $p<0.001$ (Table 4).

Subgroup-4 (Supplement Table 5, n=346) respondents (those with thyroid cancer, but no other reported co-morbidities) exhibited a similar upward trend in treatment satisfaction with DTE, although not reaching statistical significance (Table 3); perceptions about physician satisfaction also did not exhibit statistical significance between treatments. Notably, physician knowledge exhibited a downward trend, with patients on DTE ranking the lowest (4 (25^{th}-75^{th} percentile interval: 3,7). As before, the need for new treatments and impact of hypothyroidism on their lives were ranked at the highest level (Table 3). Within this group, there was a trend toward respondents taking LT4+LT3 being more likely to report weight management as a relevant area affected by hypothyroidism compared to LT4 users. There was a trend towards those taking DTE being less likely to report fatigue/low energy levels and mood issues compared to those on LT4 or LT4+LT3 (Table 4). Respondents taking DTE exhibited a trend towards being less likely to report memory problems compared to LT4+LT3 users (Table 4).

DISCUSSION

The present study reports the results of a large-scale assessment of patients' perceptions about hypothyroidism. The results suggest that dissatisfaction with hypothyroidism treatment and treating physicians are important problems for patients. Furthermore, a strong need for development of new treatments for hypothyroidism was identified. These are dramatic findings, as among physicians treatment of hypothyroidism is considered to be straightforward. The fact that the median reported satisfaction with treatment in the entire group is only 5 on a scale of 1-10 is remarkable, and even if this only reflects the situation in a small portion of patients, this is very concerning. Given that hypothyroidism is a common disease, this could translate into a significant burden of unsuccessfully resolved symptoms within the entire population. At face value, these results indicate that, although physicians believe that hypothyroidism is an eminently treatable condition, a large number of hypothyroid patients believe their lives have been greatly affected by the disease, are profoundly unhappy with their treatment, and are unhappy with their physicians. Almost universally, they believe there is a need for the development of new treatment forms. It is also remarkable that there is a clear preference for DTE in the whole group as well as when the group was broken down in multiple subgroups. Of course, the study is limited by the potential intrinsic sample bias. However, the suggestion that something "real" is being captured is bolstered by the finding that our survey did not demonstrate a clear positive patient response to synthetic combination therapy with LT4+LT3.

The present study is based on responses provided by a convenience sample that is unlikely to represent the more than 10 million Americans being treated for hypothyroidism. For example, it is likely that there is selection bias, with underrepresentation of LT4-treated patients that are not symptomatic who are less likely to be reached by thyroid-related social media. However, these results corroborate recent findings obtained from NHANES data, a population-based survey representative of individuals within the United States (a computer algorithm randomly selects households from representative regions throughout the country). Notably, the NHANES LT4-treated individuals struggled with the very same issues identified by the current sample, i.e. weight management, low energy levels, depression and poor cognition compared to age, gender and race/ethnicity matched euthyroid controls.[8,12] These differences, however, were not significantly associated with serum T3 levels, again highlighting the need to gain a better understanding of underlying mechanisms.

The focus of prior research into combination therapy has been using synthetic LT4+LT3, rather than DTE. The fourteen trials of synthetic LT4+LT3 that have been completed thus far show some patient preference for combination therapy, but have failed to show obvious superiority of LT4+LT3.[6,14-20,22-26,28] Thyroid-related symptoms were generally not improved with combination therapy, other than when TSH suppression was achieved. Parameters such as quality of life, mood, and neurocognitive performance were only improved in a minority of studies. These studies have multiple limitations (e.g. once daily dosing, short duration study, small study size, disparate TSH values between study groups) that have been previously reviewed extensively.[2,29] Failure to demonstrate superiority of LT4+LT3 could be due to any combination of these shortcomings in study design or the drug formulation. However, it is also possible that synthetic combination therapy is simply not superior to LT4. The one double blind, randomized, placebo controlled trial of DTE versus LT4 also failed to show that DTE resulted in improvement in a number of neuropsychological measures.[28] There was a preference for DTE, which was associated with the very modest, short-term weight loss of 3lbs that was associated with DTE. However, long-term, outcome data were not reported, and it is not known if the weight loss was sustained. A preference for LT4+LT3 has also been shown to be associated with the weight loss achieved during therapy, although TSH suppression was a confounding factor.[14]

If the clinical trials conducted up to now have not shown benefits of either LT4+LT3 or DTE, but uncontrolled patients surveys[27] or online patient forum opinions suggest that combination therapy is preferred, this could simply reflect biased data, or it is also possible that the appropriate patient group has not yet been formally studied. Prospective clinical trials of combination therapy have not yet been conducted that have specifically recruited dissatisfied patients, patients with the lowest circulating T3 levels; few trials have considered deiodinases or thyroid hormone transporters polymorphisms. Certainly, retrospective data suggest that patient preference may be linked to a patients' complement of thyroid hormone metabolism-associated polymorphisms.[30,31]

If DTE actually does provide more satisfactory therapy for patients with hypothyroidism, it is possible that this is due to (i) patient preference for higher treatment doses ii) patients being rendered T3-thyrotoxic, (iii) the presence of some other orally active substance other than T4 and T3 within the DTE, or (iv) a confounding factor such as use of other complementary or alternative medicine in users of DTE, or (v) an as yet unidentified aspect of thyroid physiology. It is important to keep in mind though that DTE, like LT4, does not restore normal thyroid hormone

homeostasis. Circulating levels of T3 are increased during DTE therapy and may transiently exceed the upper limits of normal, while the average blood levels of T4 are below the lower limit of normal. High levels of T3 are known to enhance mood in studies of patients with depression and it is possible that patient preference for DTE reflects a positive effect of supra-physiologic T3 levels on mood. At the same time, it is unknown whether transient supra-physiologic T3 levels are safe or whether they could promote arrhythmias, especially in older or susceptible patients. With respect to patients potentially preferring higher doses, it has recently been shown in a randomized blinded trial that patients preferred the LT4 dose that they believed was the highest dose, even if they had not identified the relative dose correctly.[32]

A major strength of this study is the large sample size. However limitations of the study include probable sampling and/or recall bias, subjectivity, a lack of an external control (e.g. patients treated for other endocrine disorders or other chronic medical conditions), and the use of an non-validated survey instrument. With respect to the first limitation, we acknowledge the increased likelihood that patients with significant dissatisfaction with their therapy for hypothyroidism are more likely to have been motivated to complete the survey than those who feel unaffected by their hypothyroidism, or even those who feel very happy about their treatment. To highlight this 50% of our survey respondents had changed their physician twice or more. It is anticipated, although not verified, that this questionnaire attracted dissatisfied patients or was preferentially publicized among groups of dissatisfied patients. We therefore anticipate that we have captured one, or possibly both, ends of the spectrum of opinion about treatment. If we assume that approximately 15% of treated patients feel worse than individuals without thyroid disease, and if we have captured a subset of these patients, our results, despite the inherent bias, nevertheless indicate a significant unmet need among patients. We also seem to have captured predominately females in our survey. We know that hypothyroidism affects women/men with a ratio of 9:1, and yet our respondents exhibited a ratio of 21:1.

With respect to the third and fourth limitations, because the diagnosis of hypothyroidism is self-reported, we cannot be sure that the respondents do not include a significant number of individuals who are taking thyroid hormone because of a misdiagnosis of hypothyroidism or for a condition other than hypothyroidism, for example fibromyalgia . Additionally, hypothyroid patients may also mistakenly attribute unrelated symptoms or decreased quality of life to their thyroid condition. Once a patient has been diagnosed with a chronic condition such as hypothyroidism, there is a natural tendency for a patient to associate their spectrum of symptoms with this condition. The attribution of these symptoms may be mistaken. If there is mis-attribution of symptoms, then these symptoms would not be expected to resolve with adjustment of therapy for hypothyroidism. It is well known that patients with hypothyroidism have a greater disease burden than the general population[6,33], and that hypothyroid patients treated to achieve a normal TSH remain symptomatic.[34,35] However, not only does manipulation of thyroid status in these individuals fail to resolve symptoms,[25,32] but also treatment of euthyroid individuals with hypothyroid-like symptoms does not resolve symptoms.[36] We attempted to mitigate these particular limitations by requesting that respondents report co-existent medical conditions and examining subgroups who did not have these conditions. In general, our findings remained generally unaltered in these subgroup analyses. However, we do not know if we have fully captured other medical conditions that might be the major source of some of the symptoms reported.

In conclusion, it is clear that a subset of patients with hypothyroidism are not satisfied with their current therapy, nor their physicians. This is unexpected. These findings highlight the need for high quality research to study treatments for hypothyroidism. Such treatments may include hormonal therapies, supportive care interventions, lifestyle modification interventions (e.g. exercise, diet), or complementary/alternative treatments. Definitive trials need to be adequately statistically powered to detect clinically significant changes in important patient outcomes, attempt to provide steady levels of T3, and specifically target individuals who are symptomatic. Failure to conduct well-designed studies to advance our understanding in this area promotes reliance on anecdotal case reports/series, self-report survey studies (such as this one), and observational registry data. In the absence of a better understanding of hypothyroidism treatment patients will continue to experience unresolved symptoms and be exposed to the risks and expenses of treatments with unproven benefits and possible harm.[37]

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567

Table 1: Demographic data, hypothyroid disease characteristics and perceptions regarding hypothyroid treatment for the total sample (n=11,166)

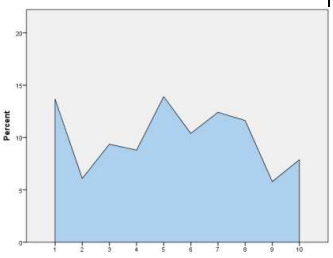
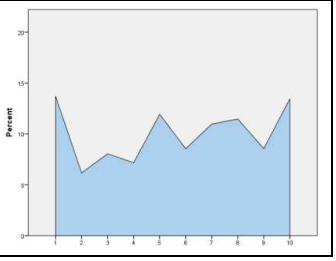
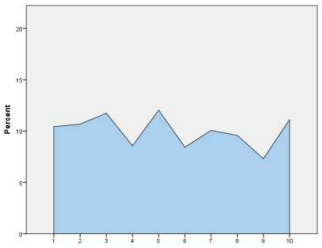
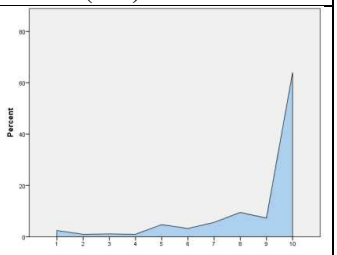
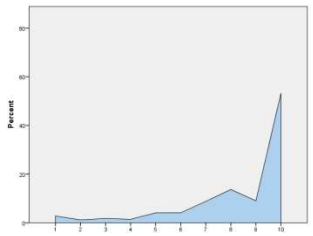
Survey section	Survey question	Possible response	Respondents
Demographics	Gender*	Female Male	10664 (96%) 502 (4%)
	Age*	31-40 years 41-50 years 51-60 years ≥61 years	2464 (22%) 3217 (29%) 2830 (25%) 2655 (23%)
Hypothyroid etiology and treatment	Etiology of hypothyroidism*	Hashimoto/autoimmune Radioactive iodine Surgery Other/Not known	4812 (43%) 858 (8%) 1694 (15%) 3802 (34%)
	What thyroid hormone are you currently taking? *	LT4 LT4 + LT3 DTE	6949 (62%) 978 (9%) 3239 (29%)
	Hypothyroid treatment duration*	Less than 1 year 1-5 years 6-10 years More than 10 years	814 (7%) 3337 (30%) 2486 (22%) 4529 (41%)
Self-reported medical history	Is a condition not related to thyroid hormone causing your symptoms?	Current stress levels Other medical problem No condition identified	3727 (33%) 3578 (32%) 3,861 (34%)
	Do you have any of these medical problems?	Heart disease Lung disease Diabetes Bone/Muscle disease GI disease Cancer (non-thyroid) Depression	510 (5%) 312 (3%) 681 (6%) 868 (8%) 1506 (14%) 243 (2%) 2965 (27%)
Perception regarding hypothyroid treatment	How satisfied are you with the treatment you receive? +	1= not satisfied 10=very satisfied	5 (3,8) 
	If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment	Weight management Fatigue or energy levels Mood Memory	7729 (69%) 8597 (77%) 5059 (45%) 6433 (58%)
	How satisfied are you with your current physician who treats you for your thyroid condition? +	1= not satisfied 10=very satisfied	6 (3,8) 

Table 1, continued			
	How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? +	1=not knowledgeable 10= very knowledgeable	5 (3,8) 
	How many times have you changed doctors because you were not satisfied with the treatment you were receiving? *	Never 1 time 2-4 times 5-9 times More than 10	3185 (29%) 1944 (17%) 4375 (39%) 1349 (12%) 313 (3%)
	How would you rate the need for new treatments for hypo-thyroidism? +	1=no need 10=strong need	10 (8,10) 
	Tried alternative hypothyroid treatment not prescribed by doctor	Yes	3108 (28%)
		No	8058 (71%)
	How has your life been affect-ed by your hypothyroidism? +	1=not affected 10=strongly affected	10 (8,10) 

* Summarized as frequency (percent)

+ Summarized as median (25th percentile, 75th percentile)

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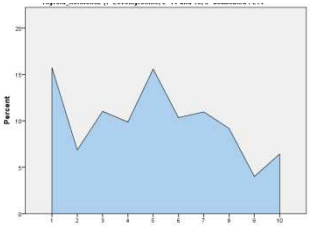
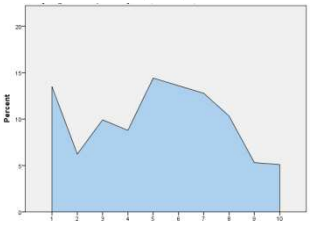
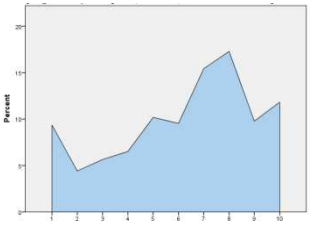
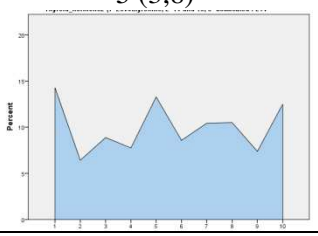
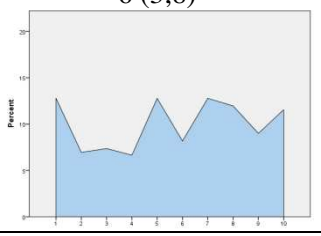
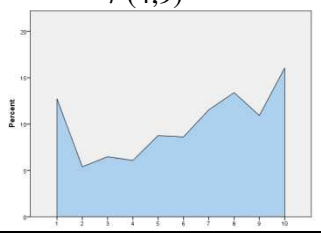
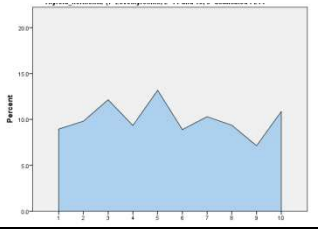
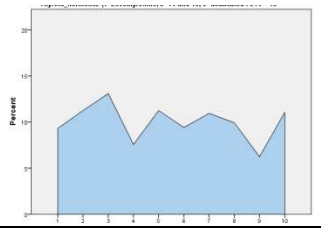
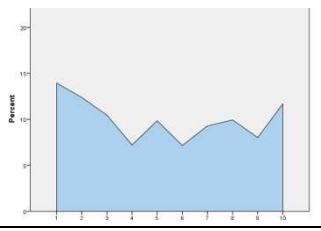
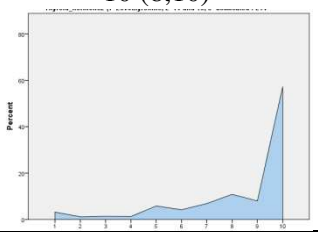
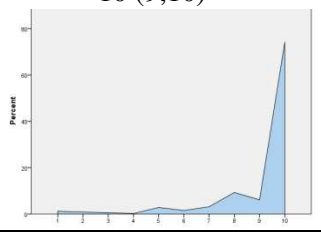
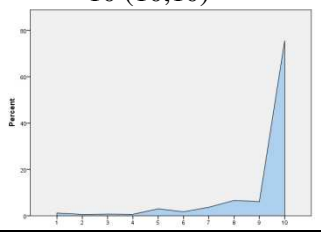
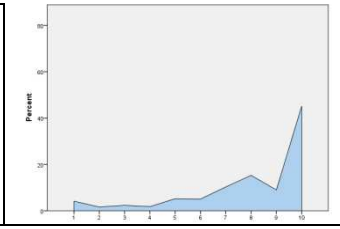
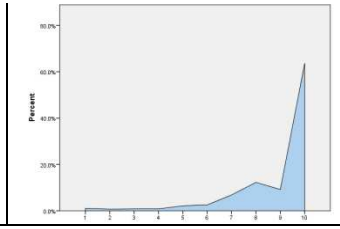
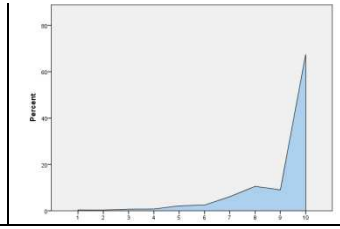
Table 2: Comparison of demographic data, characteristics of hypothyroidism and perceptions regarding hypothyroidism treatment by self-reported medication (LT4, LT4+LT3 or DTE) for the total sample (n=11,166)

Survey question	Possible response	LT4 (n=6949)	LT4+LT3 (n=978)	DTE (n=3239)	p-value
Gender*	Female Male	6546 (94%) 403 (6%)	944 (97%) 34 (3%)	3174 (98%) 65 (2%)	<0.0001
Age*	31-40 years 41-50 years 51-60 years ≥61 years	1553 (22%) 1857 (27%) 1709 (25%) 1830 (26%)	230 (23%) 286 (29%) 258 (27%) 204 (21%)	681 (21%) 1074 (33%) 863 (27%) 621 (20%)	<0.0001
Etiology of hypothyroidism*	Hashimoto/autoimmune Radioactive iodine Surgery Other	2587 (37%) 629 (9%) 1149 (17%) 2587 (38%)	475 (49%) 67 (7%) 185 (19%) 251 (12%)	1750 (54%) 162 (5%) 360 (12%) 967 (30%)	<0.0001
Hypothyroid treatment duration*	Less than 1 year 1-5 years 6-10 years More than 10 years	609 (9%) 2012 (29%) 1507 (22%) 2821 (41%)	32 (3%) 268 (27%) 245 (25%) 433 (44%)	173 (5%) 1057 (33%) 734 (23%) 1275 (39%)	<0.0001
Is a condition not related to thyroid hormone causing your symptoms?					
Do you have any of these medical problems?					
How satisfied are you with the treatment you receive? +	1= not satisfied 10=very satisfied	5 (3, 7) 	5 (3,7) 	7 (4,8)^ # 	<0.0001
If you are not satisfied, indicate relevant areas you feel are affected by your thyroid treatment*	Weight management	4889 (70%)	704 (72%)	2136 (65%)	<0.0001
	Fatigue or energy levels	5547 (80%)	793 (81%)	2257 (70%)	<0.0001
	Mood	3369 (49%)	458 (47%)	1232 (38%)	<0.0001
	Memory	4150 (60%)	612 (63%)	1671 (52%)	<0.0001

How satisfied are you with your current physician who treats you for your thyroid condition? +	1= not satisfied 10=very satisfied	5 (3,8) 	6 (3,8) 	7 (4,9) ^# 	<0.0001
Table 2, continued					
How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment? +	1=not knowledgeable 10= very knowledgeable	5 (3,8) 	5 (3,8) 	5 (2,8) 	0.012
How many times have you changed doctors because you were not satisfied with the treatment you were receiving? *	Never 1 time 2-4 times 5-9 times More than 10	2775 (39%) 1476 (21%) 2408 (33%) 456 (6%) 92 (1%)	163 (16%) 156 (15%) 481 (48%) 176 (17%) 37 (4%)	372 (11%) 407 (12%) 1636 (48%) 783 (23%) 190 (6%)	<0.0001
How would you rate the need for new hypothyroid treatments? +	1=no need 10=strong need	10 (8,10) 	10 (9,10) ^ 	10 (10,10) ^ 	<0.0001
Tried alternative hypothyroid treatment not prescribed by doctor*	Yes	1316 (19%)	309 (32%)	1483 (46%)	<0.0001
	No	5633 (81%)	669 (68%)	1756 (54%)	
How has your life been af-	1=not affected	9 (7,10)	10 (8,10) ^	10 (9,10) ^	<0.0001

fected by your hypothyroidism? +	10=strongly affected				

* Summarized as frequency (percent)

+ Summarized as median (25th percentile, 75th percentile), differences between groups determined by Kruskal-Wallis test

^ Significantly different from respondents taking LT4 by Mann Whitney U test ($p<0.0001$)

Significantly different from respondents taking LT4+T3 by Mann Whitney U test ($p<0.0001$)

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Table 3: Comparison median perception of satisfaction regarding hypothyroid treatment by self-reported medication.

SUBGROUP-1: Respondents without depression, stressors, or medical conditions	LT4 (n=2206)	LT4 +LT3 (n=316)	DTE (n=1148)	p-value
How satisfied are you with the treatment you receive?	5 (3,7)	6 (3,8)	7 (5,9) ^#	<0.0001
How satisfied are you with your current physician who treats you for your thyroid condition?	5 (3,8)	6 (3,8)	7 (4,9) ^	<0.0001
How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment?	5 (3,8)	5 (3,8)	5 (2,8)	0.04
How would you rate the need for new hypothyroid treatments?	10 (8,10)	10 (10,10)^	10 (10,10) ^	<0.0001
How has your life been affected by your hypothyroidism?	9 (7,10)	10 (9,10)^	10 (8,10) ^	<0.0001
SUBGROUP-2*:* Respondents without depression, stressors, or medical condition matched by gender, age & hypothyroid treatment	LT4 (n=614)	LT4 +LT3 (n=307)	DTE (n=614)	p-value
How satisfied are you with the treatment you receive?	5 (3,7)	6 (3,8)	7 (5,9) ^#	<0.0001
How satisfied are you with your current physician who treats you for your thyroid condition?	5 (3,8)	6 (3,8) ^	7 (3,9) ^	<0.0001
How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment?	5 (2,7)	5 (3,8)	5 (2,8)	0.05
How would you rate the need for new hypothyroid treatments?	10 (8,10)	10 (10,10) ^	10 (10,10) ^	<0.0001
How has your life been affected by your hypothyroidism?	9 (7,10)	10 (8,10)	10 (8,10)	<0.0001
SUBGROUP-3*:* Respondents with depression, but without stressors or medical conditions	LT4 (n=457)	LT4 +LT3 (n=42)	DTE (n=180)	p-value
How satisfied are you with the treatment you receive?	4 (1,6)	4 (2,6)	5 (3,7)^	<0.0001
How satisfied are you with your current physician who treats you for your thyroid condition?	5 (2,7)	5 (2,8)	6 (3,8) ^	0.001
How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment?	4 (2,6)	5 (2,7)	4 (2,8)	0.824
How would you rate the need for new hypothyroid treatments?	10 (9,10)	10 (10,10)	10 (10,10) ^	<0.0001
How has your life been affected by your hypothyroidism?	10 (8,10)	10 (10,10)	10 (10,10) ^	<0.0001
SUBGROUP-4*:* Thyroid cancer without depression, stressors, or medical conditions	LT4 (n=224)	LT4 +LT3 (n=48)	DTE (n=74)	p-value
How satisfied are you with the treatment you receive?	5 (3,8)	6 (4,8)	7 (3,8)	0.224
How satisfied are you with your current physician who treats you for your thyroid condition?	7 (4,8)	6 (3,9)	6 (2,8)	0.117
How knowledgeable is your doctor and/or physicians in general about hypothyroid treatment?	7 (4,9)	6 (4,9)	4 (3,7) ^	<0.0001
How would you rate the need for new hypothyroid treatments?	10 (7,10)	10 (10,10)	10 (10,10)	<0.0001
How has your life been affected by your hypothyroidism?	10 (8,10)	10 (10,10) ^	10 (9,10)	<0.0001

^ Significantly different from respondents taking LT4 by Mann Whitney U test (p<0.0001)

Significantly different from respondents taking LT4+T3 by Mann Whitney U test (p<0.0001)

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Table 4: Comparison of hypothyroid side-effects that are a primary concern to respondents by self-reported medication

SUBGROUP-1: Respondents without depression, stressors, or medical conditions	LT4 (n=2206)	LT4 +LT3 (n=316)	DTE (n=1148)	p-value
Weight management	69%	74%	64% #	<0.0001
Fatigue/energy levels	75%	76%	64% ^#	<0.0001
Mood	42%	40%	30% ^#	<0.0001
Memory or other problems with thinking	55%	59%	44% ^#	<0.0001
SUBGROUP-2: Respondents without depression, stressors, or medical condition matched by gender, age & hypothyroid treatment	LT4 (n=614)	LT4 +LT3 (n=307)	DTE (n=614)	p-value
Weight management	71%	74%	59%^#	<0.0001
Fatigue/energy levels	81%	77%	62%^#	<0.0001
Mood	47%	40%	29%^#	<0.0001
Memory or other problems with thinking	62%	59%	43%^#	<0.0001
SUBGROUP-3: Respondents with depression, but without stressors or medical conditions	LT4 (n=457)	LT4 +LT3 (n=42)	DTE (n=180)	p-value
Weight management	77%	71%	75%	0.690
Fatigue/energy levels	87%	93%	77%	0.002
Mood	64%	60%	58%	0.252
Memory or other problems with thinking	74%	71%	61%	0.005
SUBGROUP-4:Thyroid cancer without depression, stressors, or medical conditions	LT4 (n=224)	LT4 +LT3 (n=48)	DTE (n=74)	p-value
Weight management	59%	79%	64%	0.031
Fatigue/energy levels	77%	85%	65%	0.026
Mood	44%	50%	28%	0.028
Memory or other problems with thinking	55%	65%	45%	0.087

^ Significantly different from respondents taking LT4 by Chi-square test ($p<0.0001$)

Significantly different from respondents taking LT4+T3 by Chi-square test ($p<0.0001$)